



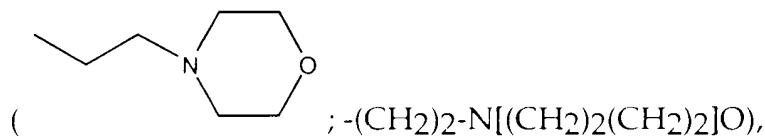
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amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil; 5-propynyluracil and the like.

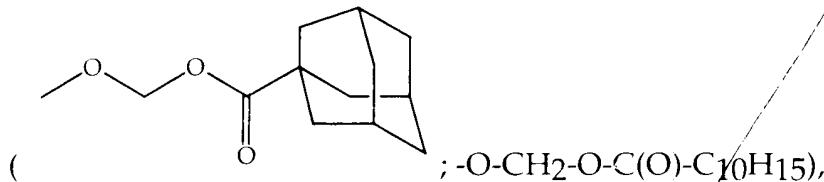
Preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-deazaadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B is a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(C<sub>1</sub>-C<sub>3</sub>-alkyl)cytosinyl.

The invention compounds, such as those of the formulas (L<sup>1</sup>)(RO)P(O)-Z-B, are optionally esterified at the phosphorus atom by the group R defined above. Exemplary R groups include phenyl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 2-, 3- and 4-pyridinyl, 2-, 4- and 5-pyrimidinyl, 2-, 3- and 4-alkoxyphenyl (C<sub>1</sub>-C<sub>12</sub> alkyl including 2-, 3- and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl), 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 2,4-dichlorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C<sub>1</sub>-C<sub>12</sub> alkyl including 2-, 3- and 4-trifluoromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 2-, 3- and 4-cyanophenyl, carboalkoxyphenyl (C<sub>1</sub>-C<sub>4</sub> alkyl including 2-, 3- and 4-carboethoxyphenyl (-C<sub>6</sub>H<sub>4</sub>-C(O)-OC<sub>2</sub>H<sub>5</sub>) and 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dicarboethoxyphenyl), 1-, 2-, 3-, and 4-pyridinyl (-C<sub>5</sub>H<sub>4</sub>N), 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C<sub>1</sub>-C<sub>12</sub> alkyl including 4-trifluoromethylbenzyl), alkylsalicylphenyl (C<sub>1</sub>-C<sub>4</sub> alkyl including 2-, 3- and 4-ethylsalicylphenyl), 2-, 3- and 4-acetylphenyl, 1,8-dihydroxy-naphthyl (-O-C<sub>10</sub>H<sub>6</sub>-OH or -O-C<sub>10</sub>H<sub>6</sub>-O-), 2,2'-dihydroxybiphenyl (-O-C<sub>6</sub>H<sub>4</sub>-C<sub>6</sub>H<sub>4</sub>-O-; both oxygen atoms are linked to the phosphorus atom), alkoxy ethyl [C<sub>1</sub>-C<sub>6</sub> alkyl including -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub> (methoxy ethyl) and phenoxyethyl], aryloxy ethyl

[C<sub>6</sub>-C<sub>9</sub> aryl (including phenoxy ethyl) or C<sub>6</sub>-C<sub>9</sub> aryl substituted by OH, NH<sub>2</sub>, halo, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkyl substituted by OH or by 1 to 3 halo atoms], -C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, N-ethylmorpholino



adamantoyl oxymethyl, pivaloyloxy(methoxyethyl)methyl  
(-CH(CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>)-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>),

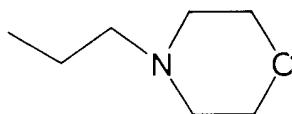


pivaloyloxymethyl (-CH<sub>2</sub>-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>), pivaloyloxy(methoxymethyl)-methyl (-CH(CH<sub>2</sub>OCH<sub>3</sub>)-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>), pivaloyloxyisobutyl (-CH(CH(CH<sub>3</sub>)<sub>2</sub>)-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>) isobutyryloxymethyl (-CH<sub>2</sub>-O-C(O)-CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>), cyclohexanoyl oxymethyl (-CH<sub>2</sub>-O-C(O)-C<sub>6</sub>H<sub>11</sub>), phenyl (-C<sub>6</sub>H<sub>5</sub>), benzyl (-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>), isopropyl (-CH(CH<sub>3</sub>)<sub>2</sub>), t-butyl (-C(CH<sub>3</sub>)<sub>3</sub>), -CH<sub>2</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>2</sub>-C<sub>13</sub>, -(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>5</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>F, -CH<sub>2</sub>-CH<sub>2</sub>Cl, -CH<sub>2</sub>-CF<sub>3</sub>, -CH<sub>2</sub>-CCl<sub>3</sub>, R<sup>5</sup>, NHR<sup>6A</sup> or N(R<sup>6A</sup>)<sub>2</sub> wherein R<sup>5</sup> is CH<sub>2</sub>C(O)N(R<sup>6A</sup>)<sub>2</sub>, CH<sub>2</sub>C(O)OR<sup>6A</sup>, CH<sub>2</sub>OC(O)R<sup>6A</sup>, CH(R<sup>6A</sup>)OC(O)R<sup>6A</sup>, CH<sub>2</sub>C(R<sup>6A</sup>)<sub>2</sub>CH<sub>2</sub>OH, or CH<sub>2</sub>OR<sup>6A</sup>, NH-CH<sub>2</sub>-C(O)O-CH<sub>2</sub>CH<sub>3</sub>, N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)O-CH<sub>2</sub>CH<sub>3</sub>, NHR<sup>40</sup>, CH<sub>2</sub>-O-C(O)-C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>-O-C(O)-C<sub>10</sub>H<sub>15</sub>, -CH<sub>2</sub>-O-C(O)-CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>-O-C(O)-CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>, CH<sub>2</sub>-O-C(O)-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>, wherein R<sup>6A</sup> is C<sub>1</sub>-C<sub>20</sub> alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms), C<sub>6</sub>-C<sub>20</sub> aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms) or C<sub>7</sub>-C<sub>20</sub> aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms), provided that for compounds of formulas N(R<sup>6A</sup>)<sub>2</sub>, CH<sub>2</sub>C(O)N(R<sup>6A</sup>)<sub>2</sub>, CH<sub>2</sub>C(O)OR<sup>6A</sup>, CH<sub>2</sub>OC(O)R<sup>6A</sup>, CH(R<sup>6A</sup>)OC(O)R<sup>6A</sup> and CH<sub>2</sub>C(R<sup>6A</sup>)<sub>2</sub>CH<sub>2</sub>OH, the total number of carbon atoms present is less than 25 (preferably the number of carbon atoms present is about 4 to about 14) and R<sup>40</sup> is C<sub>1</sub>-C<sub>20</sub> alkyl.

Exemplary R groups include X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, R<sup>5</sup>, NHR<sup>6A</sup> and N(R<sup>6A</sup>), wherein  
X<sup>1</sup> is selected from the group consisting of 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl and 2-, 4- and 5-pyrimidinyl;

X<sup>2</sup> is selected from the group consisting of phenyl, benzyl, -C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, 2-, 3- and 4-alkoxyphenyl (C<sub>1</sub>-C<sub>12</sub> alkyl including 2-, 3- and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl), 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 2,4-dichlorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C<sub>1</sub>-C<sub>12</sub> alkyl including 2-, 3- and 4-trifluoromethylphenyl and 2-, 3-, and 4-trichloromethylphenyl), 2-, 3- and 4-cyanophenyl, carboalkoxyphenyl (C<sub>1</sub>-C<sub>4</sub> alkyl including 2-, 3- and 4-carboethoxyphenyl (-C<sub>6</sub>H<sub>4</sub>-C(O)-OC<sub>2</sub>H<sub>5</sub>) and 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dicarboethoxyphenyl), 2-, 3-, and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms (C<sub>1</sub>-C<sub>12</sub> alkyl including 4-trifluoromethylbenzyl), alkylsalicylphenyl (C<sub>1</sub>-C<sub>4</sub> alkyl including 2-, 3- and 4-ethylsalicylphenyl), 2-, 3- and 4-acetylphenyl, phenyl substituted by methoxy, ethoxy, OH, NH<sub>2</sub>, halo, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkyl substituted by OH or by 1 to 3 halo atoms, and -C<sub>10</sub>H<sub>6</sub>OH; and

X<sup>3</sup> is selected from the group consisting of alkoxy ethyl (C<sub>1</sub>-C<sub>6</sub> alkyl including -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>),



adamantoyloxymethyl, pivaloyloxy(methoxyethyl)methyl

(-CH(CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>)-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>}, 1-adamantane-  
carbonyloxymethyleneoxymethyl-, pivaloyloxymethyl (-CH<sub>2</sub>-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>),  
pivaloyloxy(methoxymethyl)-methyl (-CH(CH<sub>2</sub>OCH<sub>3</sub>)-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>,  
pivaloyloxyisobutyl (-CH(CH(CH<sub>3</sub>)<sub>2</sub>)-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>), isobutyryloxymethyl  
(-CH<sub>2</sub>-O-C(O)-CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>), cyclohexanoyloxymethyl  
(-CH<sub>2</sub>-O-C(O)-C<sub>6</sub>H<sub>11</sub>), isopropyl (-CH(CH<sub>3</sub>)<sub>2</sub>), t-butyl (-C(CH<sub>3</sub>)<sub>3</sub>),  
-CH<sub>2</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>5</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-  
CH<sub>2</sub>F, -CH<sub>2</sub>CH<sub>2</sub>Cl, -CH<sub>2</sub>-CF<sub>3</sub> and -CH<sub>2</sub>-CCl<sub>3</sub>;

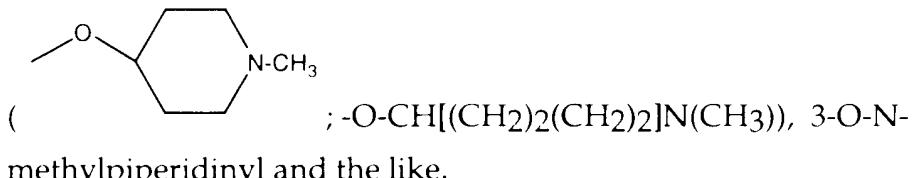
or two R groups are joined to form substituents selected from the group  
consisting of -C<sub>10</sub>H<sub>6</sub>- and -C<sub>6</sub>H<sub>4</sub>C<sub>6</sub>H<sub>4</sub>-,

wherein R<sup>5</sup> is selected from the group consisting of CH<sub>2</sub>C(O)N(R<sup>6A</sup>)<sub>2</sub>,  
CH<sub>2</sub>C(O)OR<sup>6A</sup>, CH<sub>2</sub>OC(O)R<sup>6A</sup>, CH(R<sup>6A</sup>)OC(O)R<sup>6A</sup>, CH<sub>2</sub>C(R<sup>6A</sup>)<sub>2</sub>CH<sub>2</sub>OH,  
CH<sub>2</sub>OR<sup>6A</sup>, NH-CH<sub>2</sub>-C(O)O-CH<sub>2</sub>CH<sub>3</sub>, N(CH<sub>3</sub>)-CH<sub>2</sub>-C(O)O-CH<sub>2</sub>CH<sub>3</sub>, NHR<sup>40</sup>,  
CH<sub>2</sub>-O-C(O)-C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>-O-C(O)-C<sub>10</sub>H<sub>15</sub>, -CH<sub>2</sub>-O-C(O)-CH<sub>2</sub>CH<sub>3</sub>,  
CH<sub>2</sub>-O-C(O)-CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>-O-C(O)-C(CH<sub>3</sub>)<sub>3</sub>, and CH<sub>2</sub>-O-C(O)-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>;

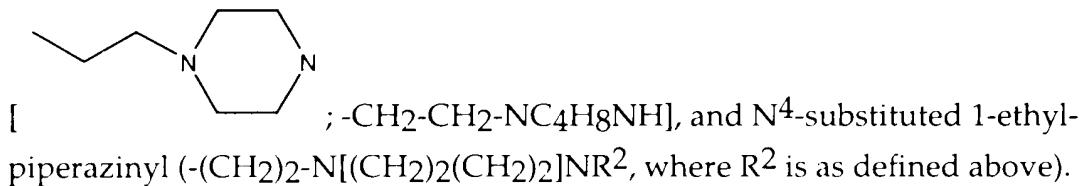
wherein R<sup>6A</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>20</sub> alkyl which  
is unsubstituted or substituted by substituents independently selected from the  
group consisting of OH, O, N and halogen (1 to 5 halogen atoms), C<sub>6</sub>-C<sub>20</sub> aryl  
which is unsubstituted or substituted by substituents independently selected  
from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms) or C<sub>7</sub>-  
C<sub>20</sub> aryl-alkyl which is unsubstituted or substituted by substituents  
independently selected from the group consisting of OH, O, N and halogen (1 to  
5 halogen atoms), wherein O and N are substituted for carbon and provided that  
the total number of R<sup>5</sup> or R carbon atoms is less than 25 (preferably about 4 -  
about 14) for compounds where R<sup>5</sup> or R is selected from the group consisting of  
N(R<sup>6A</sup>)<sub>2</sub>, CH<sub>2</sub>C(O)N(R<sup>6A</sup>)<sub>2</sub>, CH<sub>2</sub>C(O)OR<sup>6A</sup>, CH<sub>2</sub>OC(O)R<sup>6A</sup>,  
CH(R<sup>6A</sup>)OC(O)R<sup>6A</sup> and CH<sub>2</sub>C(R<sup>6A</sup>)<sub>2</sub>CH<sub>2</sub>OH; and

wherein  $R^{40}$  is  $C_1$ - $C_{20}$  alkyl.

The invention compounds are optionally alkylated at the  $\alpha$ -nitrogen atom of the amino acid by the  $R^1$  group defined above. Exemplary  $R^1$  groups include H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, benzyl, 4-O-N-methylpiperidinyl



The invention compounds are optionally esterified at the amino acid carboxyl moiety by the  $R^4$  group defined above. Exemplary  $R^4$  groups include H, methyl, ethyl, propyl, isopropyl, butyl, t-butyl (C(CH<sub>3</sub>)<sub>3</sub>), phenyl (-C<sub>6</sub>H<sub>5</sub>), benzyl (-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>), 1-pyridyl, 3-pyridyl, 1-pyrimidinyl, N-ethylmorpholino (-CH<sub>2</sub>-CH<sub>2</sub>-N[(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>]O), N-2-propylmorpholino (-CH(CH<sub>3</sub>)-CH<sub>2</sub>-N[(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>]O), methoxyethyl (-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>), 4-N-methylpiperidyl (-CH[(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>]N(CH<sub>3</sub>)), 3-N-methylpiperidyl, phenol which is 2-, 3-, or 4-substituted by N(R<sup>30</sup>)<sub>2</sub> where R<sup>30</sup> is independently H or  $C_1$ - $C_6$  alkyl unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, COOR<sup>4</sup> and halogen or  $C_6$ - $C_{12}$  aryl unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, COOR<sup>4</sup>, N(R<sup>7</sup>)<sub>2</sub> and halogen (including 2-, 3-, and 4-N,N-dimethylaminophenol and 2-, 3-, and 4-N,N-diethylaminophenol), 1-ethylpiperazinyl



Additional compounds that are included in the invention are nucleotide analog dimers that are linked via an amino or carboxyl group. As used herein, dimers (or trimers) refer to the presence of two (or three) nucleoside residues that comprise a compound. Thus, a -L<sup>1</sup>-P(O)(L<sup>1</sup>)-Z-B or -P(O)(L<sup>1</sup>)-Z-B radical covalently linked to a -L<sup>1</sup>-P(O)(L<sup>1</sup>)-Z-B or -P(O)(L<sup>1</sup>)-Z-B radical gives B-Z-P(O)(L<sup>1</sup>)-P(O)(L<sup>1</sup>)-Z-B, B-Z-P(O)(L<sup>1</sup>)-L<sup>1</sup>-P(O)(L<sup>1</sup>)-Z-B or B-Z-P(O)(L<sup>1</sup>)-L<sup>1</sup>-P(O)(L<sup>1</sup>)-Z-B.